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"PROCEDURE TO PREPARE 3-HI-DROXY-5-(1- POLYAZOLYL)-2-METHOXYCARBONYLTIOPHEN DERIVATIVES"

[PROCEDIMIENTO PARA LA PREPARACIÓN DE DERIVADOS DE 3-HIDROXI-5- (1-POLIAZOLIL)-2-METOXICARBONILTIOFENOS]

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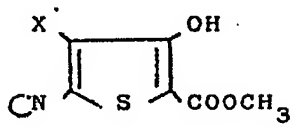
DESCRIPTIVE REPORT

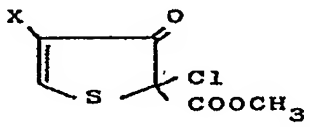
This invention relates to a procedure used to prepare a series of compounds characterized by general formula I that may be useful as intermediate or final products in the synthesis of new therapeutic agents,



I

wherein X represents a hydrogen or halogen atom and  signifies any polyazolic or benzopolyazolic heterocycle.

The procedure, to which this invention relates, is characterized by the fact that the compounds, which structure responds to the following general formula (II)



II

and wherein X represents a hydrogen or halogen atom resulting from 3-hydroxy-2-methoxycarbonyltiophen or any of its halogen 4 derivatives by means of a method previously described, react at room temperature with twice the amount

of a polyazolic or benzopolyazolic heterocycle in the presence of a solvent, producing the compounds of general formula I.

In every case, the reaction occurs by adding 1.4 of the NH group of the heterocycle to the α,β-enonic system of compounds II and subsequent spontaneous loss of hydrogen chloride resulting from the elimination of γ, which is collected by the excess of heterocycles present in the reaction, producing compounds I.

It shall be easily understood that these stages that constitute the essential features of the invention, may take place using solvents, reagents, catalysts and a variety of experimental conditions, which are obvious to any specialist. Consequently, any logical modification of these factors must be considered as included in the essential features of the invention.

Therefore, the conditions presented in the examples, although preferred for practical reasons, must not be considered as the only ones used or claimed in this invention.

EXAMPLE 1

Preparation of 3-hydroxy-5-(1-pyrazolyl)-2-methoxycarbonyl-tiophen

(I, X=H, =1-pyrazolyl)

1.2g (0.018 moles) of pyrazole were added to a solution of 1.7g (0.009 moles) of 2-chloride-methoxycarbonyl-3-oxo-2,3-dihydrotiophen (II, X=H) in 10 ml of acetic acid. The reaction mixture was left for 2 days at room temperature and the crystallized solid was filtered and washed with acetic acid, obtaining a colorless solid with a melting point of 161 - 163°C. The concentration of the bittern allowed a greater amount of this solid to be obtained.

A sample was recrystallized from acetic acid, increasing the melting point to 162 -164°C.

Analysis (%)

Calculated for $C_9H_8N_2O_3S$	C 48.21	H 3.57	N 12.50
Found	48.37	3.71	12.63

EXAMPLE 2

Preparation of 3-hydroxy-5-(1-imidazolyl)-2-methoxycarbonyl-tiophen.

(I, X=H,  = 1- imidazolyl)

0.35 g (0.052 moles) of imidazole dissolved in 3 ml of chloroform was added to a solution of 0.5 g (0.0026 moles) of 2-chloride-2-methoxycarbonyl-3-oxo-2,3-dihydrotiophen (II, X=H) in 3 ml of chloroform. The reaction mixture was left for 2 days at room temperature and it completely evaporated. The residue was treated with water and benzene and a solid, which recrystallized from ethyl acetate or acetic acid, was obtained from the evaporation, which occurred during the benzene stage. Melting point: 112-113°C.

Analysis (%)

Calculated for	$C_9H_8N_2O_3S$	C 48.21	H 3.57	N 12.50
Found		48.49	3.71	12.39

EXAMPLES 3 - 10

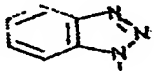
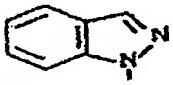
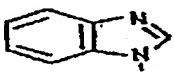
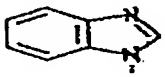
Starting with 2-chloride-2-methoxycarbonyl-3-oxo-2,3-dihydrotiophen (II, X=H) or its chloride derivative (II, X-Cl) and applying the same experimental conditions as in

example 1, the products indicated in the Table were obtained.

EXAMPLES 11 - 13

Starting with 2-chloride-2-methoxycarbonyl-3-oxo-2,3-dihydrotiophen (II, X=H) or its chloride derivative (II, X-Cl) and applying the same experimental conditions as in example 2, the products indicated in the Table were obtained.

TABLE

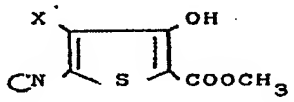
Ex. N°	N	X	P.F. (°C)		Analysis %C	%H	%N
3		Cl	136-138[a]	Calculated Found	41.77 41.83	2.71 3.00	10.83 11.07
4		H	166-167[b]	Calculated Found	42.66 42.51	3.11 3.07	18.66 18.48
5		Cl	171-173[a]	Calculated Found	36.99 37.13	2.31 2.56	16.18 16.33
6		H	185-187[b]	Calculated Found	52.36 52.08	3.27 3.21	15.27 15.43
7		Cl	144-146[b]	Calculated Found	46.53 46.71	2.58 2.73	13.57 13.46
8		H	183-185[b]	Calculated Found	56.93 57.09	3.65 3.56	10.22 10.43
9		Cl	194-196[b]	Calculated Found	50.57 50.65	2.92 2.86	9.08 9.41
10		H	211-213[b]	Calculated Found	47.24 47.07	3.94 4.12	11.02 11.31
11		Cl	173-175[a]	Calculated Found	41.78 41.93	2.71 2.87	10.83 11.02
12		H	90-92[b]	Calculated Found	56.93 57.12	3.65 3.49	10.22 10.31
13		Cl	144-146[b]	Calculated Found	50.57 50.71	2.92 3.05	9.08 9.17

a. Recrystallized from methanol. b. Recrystallized from acetic acid.

CLAIMS

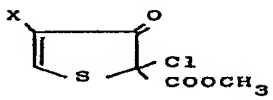
As a new invention, the property and exclusive rights for the exploitation hereof are claimed:

1) "PROCEDURE TO PREPARE 3-HI-DROXY-5-(1-POLYAZOLYL)-2-METHOXYCARBONYLTIOPHENS DERIVATIVES" of the following general formula:



II

wherein X represents a hydrogen or halogen atom and signifies any polyazolic or benzopolyazolic heterocycle, characterized by the fact that the compounds, presenting the following general formula:



II

wherein X represents a hydrogen or halogen atom, react at room temperature with twice the amount of a polyazolic or benzopolyazolic heterocycle of formula  , in the

presence of a solvent, producing the compounds of general formula I.

2) A procedure according to claim 1 characterized for using 2-chloride-2-methoxycarbonyl-3-oxo-2,3-dihydrotiophen as starting material.

3) A procedure according to claim 1 characterized for using 2,4-dichloride-2-methoxycarbonyl-3-oxo-2,3-dihydrotiophen as starting material.

4) A procedure according to claim 1 characterized for using the pyrazole as a reacting heterocycle.

5) A procedure according to claim 1 characterized for using 1,2,4-triazole as a reacting heterocycle.

6) A procedure according to claim 1 characterized for using imidazole as a reacting heterocycle.

7) A procedure according to claim 1 characterized for using benzotriazole as a reacting heterocycle.

8) A procedure according to claim 1 characterized for using indazole as a reacting heterocycle.

9) A procedure according to claim 1 characterized for using benzimidazole as a reacting heterocycle.

10) "PROCEDURE TO PREPARE 3-HI-DROXI-5-(1-POLYAZOLYL)-2-METHOXYCARBONYLTIOPHENS DERIVATIVES" as described in the body of this descriptive report and claims consisting of 7 pages, written on only one side.

Madrid, September 30, (illegible)

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